PUBLIC POLICY AND REGULATION*

Panel Discussion

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MALCOLM MACKAY. Would any member of the panel like to comment on the prepared remarks of any other panelist?

MARVIN E. EISENSTADT. In this country today the average person, that is, averaging both the saccharin and nonsaccharin user, uses less than half an ounce of saccharin a year. He uses 120 pounds of sugar a year and to duplicate that Canadian study you would have to take in 145 pounds of saccharin a year. The second point I would like to make is that the experiments with saccharin have not affected monkeys, mice, or rats. They have only affected one strain of rat, the Charles River rat. They produced no type of tumor in any other animal, and in the Charles River rat the tumor was only in the bladder. That leads many scientists to question the finding. Why is this?

DR. I. BERNARD WEINSTEIN. I think that historical experience would indicate that the animal screening system is relatively reliable. We have nothing more reliable to go on. Every known human carcinogen, with the exception of arsenic, has produced tumors in mice or rats. In several cases the animal system has predicted agents that eventually proved to be carcinogenic in the human, in some cases even the histologic types of tumors that would occur in the human. Now, the reverse cannot be said with equal certainty. We know of at least a few hundred chemical carcinogens. Not all of them have been proved to be human carcinogens, but that

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might represent limitations of the human data. So there is a rather good correlation, which I think one must keep in mind.

Mr. Eisenstadt's second point is the question of dosage in animal bioassays. This reflects practical limitation in terms of the number of animals it is feasible to use. For practical purposes, one cannot use more than 50 to 100 animals per test. If fewer than five or 10 animals get tumors, the results may not be statistically significant. Yet we want to detect agents that produce even a low cancer incidence, say 1% or less, because a 1% incidence in the human population would be a major health hazard. The usual solution to this dilemma is to increase the dose given to the test animals so that a larger number of tumors might be induced and then attempt to extrapolate to what would happen at lower doses. We must also fully recognize, however, the limitations of raising the dose and the assumptions associated with dose extrapolation; we have heard here the reservations about this approach. On the other hand, there is no reason to believe that this approach is totally false. Let me give you an example. If in a rat bioassay the dose of saccharin were 1,000 times that of human consumption and the agent induced a 10% tumor incidence then, given a population of 200,000,000 Americans at risk, that could be comparable to about 20,000 human cancers. I use that number only as an example. I am not saying that 20,000 Americans will get cancer from saccharin, but that if we use a linear dose-response extrapolation and correct for the 1,000-fold dose, that would be the predicted number. Scientists and society have to decide, first, whether they believe in linear extrapolation and, second, whether 20,000 potential new cancers is an acceptable risk.

MR. EISENSTADT. First of all, saccharin has only been tested at the 5% level. When they go to 2 1/2% or 1%, there is no cancer; it is only at the 5% level. Now, about linear extrapolation: The American Society of Bariatric Physicians, which studies overweight people and which is very much in favor of saccharin as a tool to help diabetics, has come out with an answer to that type of reasoning. Based on information on second-generation male rats, the Food and Drug Administration says that no more than 1,200 cases of bladder cancer would occur if every person in the United States consumed one large diet soft drink a day. However, only half of the United States population is male, hence, in males the maximum would be 600 cases. However, incidence of benign tumors represented one third of the total, so it goes on and on this way and it is reduced to 113 cases rather than 1,200. There is an old saying, "Figures lie and liars

figure." This extrapolation can be carried only so far. The only thing I am saying is that at 5%, which could very well be above the maximum tolerated dose of the rat, you seem to have some kind of a problem. At any lesser level you do not. Now, if saccharin were as toxic as aflotoxin is, if you used less than one quarter of 1% every rat would die. Then you would bring it down to 3% or 2% and it would be considered fine.

DR. WEINSTEIN. The argument that you only see it at a 5% level and not at a lower level simply can be a matter of statistics. You are looking for the incidence in a very small population. If you take one of the largest tests, say one from the National Cancer Institute or any other test, we start with 100 animals. One must see statistical significance in the response. Now there are 100 animals for 200,000,000 people—roughly, one animal to two million people. When we talk about the incidence of cancer in the American population, we are not talking about accepting things on the order of 5 or 10% incidence. That is an enormous increase. We are looking for very small incremental increases. That one tests something at 5% and gets a response, and tests it at a lower percent and does not, does not mean that that is a safe level or that if one increased the number of animals appropriately one would see a response. The limitation is in doing such tests—an average National Cancer Institute test using about 100 animals at different levels costs us $200,000 to $300,000. We do not have the resources to use 1,000, 10,000, 100,000, or 1,000,000 just to look for effects. The smaller the population you are examining for a response, the higher has to be the dose and that is what the experiment simply reflects. One cannot conclude that simply because at below 5% one sees nothing then nothing is occurring.

MR. EISENSTADT. In this particular situation—where you are dealing with a substitute that, if banned, leaves nothing but sugar—the expense of using 1,000 rats should be accepted to go down to 2%

DR. WEINSTEIN. Let me respond to that. I think that we have lost one point here. The FDA now suggests that involuntary exposure such as in toothpaste and all sorts of foods and beverages be eliminated. If saccharin can be shown to be safe and efficacious as an over-the-counter drug for diabetics, its sale may be continued. I would suggest that most of the saccharin used in this country is not used by diabetics, but by people who think they can lose weight by using these substitutes.

JOHN R. QUARLES, JR. We have just witnessed a very erudite discussion of some of the intricacies of animal testing, how it must be done, and what

it means. Whether it is necessary to go to these high rates or whatever they mean, one must recognize that under the formulas by which the FDA works because of the Delaney clause, whenever it is found that animals develop cancer, it drives the conclusion all the rest of the way. One does not take into account whether the results in one species are likely to be reproduced in another species.

DR. A. KARIM AHMED. The implication is that every time a tumor results from an animal experiment the government has no choice but to ban the agent. I disagree. I do not think the government is that precipitous in its action. In fact, it is very slow in acting and speaking; it takes a long time.

DR. ROY E. ALBERT. I want to point out that the Delaney clause, being a yes or no operational instrument, requires that the flexibility be directed at the issue of whether or not the agent is a carcinogen. That puts it up to the scientists to make the judgments. Other laws and other agencies take different approaches. For instance, in the Environmental Protection Agency, particularly with pesticides, the approach has been to look at the evidence in terms of a warning signal that the agent could be a human carcinogen, and in some instances the signal comes through loud and clear where they have obvious human evidence plus backup with animal evidence. In some cases the picture is murky and very muddled. This involves, then, both making a judgment as to the likelihood that the agent is a human carcinogen and an estimate, however crude, of the magnitude of the impact given the magnitude of the exposure— with a strict separation between the assessment of risk and the assessment of socioeconomic impact so that these factors are studied separately and then synthesized.

I think that in the case of saccharin there is not enough separation between the characterization of the risk and balancing that against the socioeconomic impact. It seemed to me that on the basis of the state of the art there is no question that animal data constitute a signal that cannot be ignored and that saccharin could be a human carcinogen. Starting with that—which seems to me an inescapable judgment—then one could look at the other issues and strike some balances. I think the reactions people have are, or at least should be, not to focus on the uncertainties in the test, because even though they are substantial the test results cannot be dismissed.

DR. JOSEPH H. HIGHLAND. Smoking is a personal choice, but I do not want chemicals being put in my food, my air, my water, my toothpaste, or anything else, and I think that society may have to make some judgments

about what exposures it wants to control. That should not be confused with individual voluntary decisions. The FDA has said that the Delaney Amendment and other provisions of the Food, Drug and Cosmetic Act prevent the use of saccharin, as a carcinogen, in food. It has now allowed an alternative, which would allow the kind of personal choice that has been mentioned—permitting use of the chemical as an over-the-counter drug for diabetics or whoever else wants it.

MR. LAWRENCE J. AHERN. I am sure we are all aware of the realities of politics. We all know that the government subsidizes tobacco growers. Certainly it has not acted in terms of tobacco. The question is why not? Tobacco is not a pure drug, but it might be construed as a toxic substance, as an instrument that violates the Clean Air Act. My question, then, is one I have been waiting to ask for years: Is there an existing regulation which would cover the banning of tobacco? If not, why not? If there are such laws, what steps are being taken to implement or to block these laws?

MR. QUARLES. A point which I think most important is that we are in a changing period in regard to our understanding of cancer. A short while ago we had very little understanding of what caused cancer and very few substances really could be labeled with some degree of confidence as either carcinogens or even suspected carcinogens. Now that is totally changed and hundreds upon hundreds of substances have either been demonstrated as human or animal carcinogens or are suspected as carcinogens to one or the other. The decisions which society has to make are going to be complicated, costly, and painful. It seems to me that the only basis upon which the necessary adjustments can work is by some broad, public understanding of how these decisions are being made.

My quarrel with the Delaney clause is not that you ought to allow cancer-causing substances to be put in food. My quarrel with it is based upon the point that Dr. Roy Albert brought out, that it places all discretion in the scientific judgment whether there is a carcinogen. The reality is that other factors have to be considered—the benefits, the risks, the levels of exposure, and all the rest—so those factors creep into the decision. After the decision has been made, the person who has to announce and explain that decision cannot explain it in terms a common citizen can understand. The way the Delaney clause influences the phrasing of the decision causes the understanding of the public to get twisted into a misunderstanding. The Delaney clause will not survive the next 10 years.

DR. HIGHLAND. I think the public response to the use of the Delaney

clause in terms of the saccharin ban is a clear example of what can be done correctly and what can be done incorrectly. The first announcement was handled very badly. It gave the public no understanding. It talked about 800 bottles or 1,200 bottles of soda a day. It did not attempt to explain the reasons for such high doses and how it is properly used. The subsequent announcement by Commissioner Donald Kennedy went a long way to correct those shortcomings, but there is a clear difference if the agency wants to do things the right way or does not care to do them the right way. What the FDA did initially clearly was bound to stir up a turmoil in the population. It was not explained correctly. It was a very bad presentation. Agency announcements have to aid public understanding rather than confuse it. I think that can be done.